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MEMORANDUM

Re: 1st Annual SRNT Conference

The Society for Research on Nicotine and Tobacco held its first annual scientific conference in San Diego, California on March 24-25, 1995. The meetings included presentations by Dr. Neil Benowitz, Dr. Jack Henningfield, Dr. John Hughes, and Dr. Lynn Kozlowski. This memorandum summarizes the highlights of the two-day conference.[1/]

I. Introduction and Overview.

The scope of the SRNT conference was quite broad, with presentations addressing historical, scientific, and public policy issues relating to nicotine. Several sessions focused largely, if not completely, on political issues associated with smoking in the United States.

There were no major scientific breakthroughs announced at the conference, although a number of researchers presented data that were claimed to support existing understandings regarding the effects of nicotine on the human central nervous system. On balance, both conference presenters and attendees raised more scientific questions about nicotine and smoking than they answered.

1/ In addition, many of the session were tape recorded. I have the cassettes for the Forum on the Control of Tobacco Products. Recordings of the other sessions are on order.

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With regard to public policy issues, several presenters, many with ties to NIDA or similar institutions, argued in favor of additional restrictions on the manufacture, distribution, sale, and consumption of tobacco products. Most of the proposals were not new, and included such suggestions as raising taxes on tobacco products, imposing advertising bans on tobacco products, revising the FTC testing method, requiring new and larger warning labels on tobacco product packaging, providing access to tobacco products by prescription only, and regulating the nicotine content of tobacco products.

Perhaps most significantly -- and suprisingly -- Dr. Neil Benowitz expressed a receptiveness to the idea of using low "tar"/high nicotine cigarettes as a possible alternative regulatory approach to government-mandated de-nicotinized cigarettes. However, his support for this idea was not unqualified.

II. Opening Session.

Dr. Ovide Pomerleau, current President of the SRNT, opened the conference with brief comments on the importance of nicotine studies. He emphasized the growth in the field of nicotine studies, and expressed the hope that there would be many more SRNT conferences to follow. Dr. Pomerleau's remarks did not include any substantive matters.

Dr. Ed Domino then made a presentation on the history of nicotine and nicotine studies. His presentation was primarily historical in nature, and included detailed

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descriptions of "tobacco narcosis as an important aspect of shamanism." He continued his history lesson with references to Columbus and Raleigh.

Moving into the 20th century, Domino described the invention of the first cigarette-making machine in Richmond, Virginia, and the increase in the prevalence of smoking following World War I. He adverted to the 1964 and 1988 Surgeon General's Reports, and mentioned the Castano suit in Louisiana.

Domino spoke briefly about the pharmacologic effects of nicotine, asserting that data exist supporting two incompatible theses regarding its use: (1) nicotine works as a stimulant in the brain, and (2) nicotine merely normalizes brain function in smokers. Domino said that additional research was needed to determine which theory best describes nicotine's principal effect.

In closing, Domino called nicotine a "fleur du mal" and asked rhetorically whether we could give it up. He suggested that prohibition would not work, but that "clinical objectivity" was needed to unlock nicotine's secrets: "Damn the torpedoes and full speed ahead in the pursuit of excellent science."

John Hughes followed Domino, and spoke about the present and future of nicotine research. He described a 200% growth rate in academic publishing about nicotine during the period 1970-1995. Hughes also warned that "external

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pressures" were being brought to bear on scientists working in the field of nicotine research.

Hughes then presented an update on the clinical treatment of smokers trying to quit, using a "good news/bad news" format. The "good news" included: "an empirical focus" in nicotine research, "good collegiality among nicotine researchers," and "more media coverage." He also noted that funding for nicotine research was good, and improving, with grants available from NIDA, NCI, and other government entities, in addition to private foundations and pharmaceutical companies.

According to Hughes, the "bad news" included: "very low quit rates," difficulty in "relapse prevention," only a "20-30% quit rate using nicotine replacement therapy," and "post-cessation weight gain." He expressed disappointment with the results of nicotine replacement therapy, noting that "[n]icotine replacement therapy should have a big effect, but there has not been any big movement."

Hughes concluded by urging clinicians to "tailor their treatment to subgroups within the population." He also emphasized the importance of "getting patients into treatment."

III. <u>Keynote Address.</u>

Dr. Jesse Steinfeld, former U.S. Surgeon General, presented the keynote address. His comments were largely

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anecdotal, and focused on his efforts to start a "non-smokers' rights" program in the early 1970s.

Steinfeld began his remarks by recounting that in the 1960s, tobacco companies sent representatives to FDA-sponsored meetings regarding the effects of nicotine. Without much of a transition, he then alleged that tobacco companies manipulate the level of nicotine in cigarettes and stated that the FDA's Commissioner has the authority to regulate "an ingenious device for delivering nicotine." However, Steinfeld stated that should David Kessler do this, "he would be fired."

He used this hypothetical to segue into a discussion of a meeting in 1977, at which he said that Peter Boren committed the Carter administration to a strong anti-tobacco policy. Steinfeld claimed that Boren later recanted on this promise, and suggested that Boren's behavior was a function of the politics of tobacco.

Steinfeld concluded by proposing a number of steps to better define the role of the government in tobacco control health policy, including: (1) support for basic and social research, (2) higher taxes on tobacco products, (3) abolition of price supports for tobacco, (4) a complete ban on the advertising of cigarettes, and (5) "the FDA should take a chance and regulate cigarettes."

IV. <u>Forum on the Control of Tobacco Products.</u>

This session addressed proposals for the reduction or elimination of tobacco products in the United States. It

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featured presentations by Benowitz, Henningfield, Hughes, and Kozlowski, in addition to remarks by Charles Gruder, who heads the California Tobacco-Related Disease Research Program, a Proposition 99-related entity.

A. Henningfield

Dr. Henningfield began by claiming that tobacco smoking causes 400,000 deaths annually and $70 billion in increased medical costs. He argued that in light of these facts, "the current regulatory regime reflects a turn-of-the century mentality." According to Henningfield, the government's current practices "make it easy to get the disease and hard to get treatment."

Henningfield continued by recounting David Kessler's efforts at regulating tobacco products in 1994. He expressed regret at the change in the regulatory milieu following the November 1994 elections.

He then moved to a critique of the FTC testing methodology, arguing that ventilation holes and individual smoking patterns make the FTC numbers "useless." He suggested that the FTC numbers "could be replaced with labels that provide the public with substantially more useful information."

Henningfield concluded by setting forth proposals for "reform" of current public policies on smoking and tobacco products. He suggested expanded labelling requirements and imposing broader regulations on the content of cigarettes.

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Among the broad alternative strategies he proposed were: (1) banning tobacco products, (2) making tobacco products available only by prescription, (3) and expanding current control programs. He also suggested that the FDA should undertake several specific initiatives to: (1) restrict access to tobacco products, (2) limit marketing of tobacco products, (3) increase access to tobacco replacement therapies, and (4) discourage youth smoking.

B. Kozlowski

Lynn Kozlowski's presentation, entitled "Informing Smokers About Cigarettes: Dancing With the Devil or Protecting Consumers," focused on labelling and advertising issues. Kozlowski argued that the current labelling includes comforting words (e.g., "light," "ultra-light") that do not reflect the product's content or effects. He also complained that the four rotating warnings are "weak" and "legalistic." Kozlowski suggested that the United States should adopt labelling requirements similar to those used in Canada.[2/]

Kozlowski then turned to the FTC testing method, which he denounced. He advocated a new testing method, which would determine the overall potential yield levels for nicotine, "tar," and carbon monoxide. According to Kozlowski, manufacturers should be required to provide consumers with a

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2/ Representative Canadian warnings include: "Cigarettes Are Addictive," "Smoking Can Kill You," "Tobacco Smoking Causes Fatal Lung Disease," and "Tobacco Smoking Can Harm Your Children." In Canada, these warnings appear is very large print on the front of cigarette packages.

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range of yields, rather than a single number. This information should be easy to understand, he said, and should appear prominently on the packaging for cigarette products. He showed a slide of "Craven" cigarettes, a brand from Australia. The package had a color scale, which compared filter color to nicotine/"tar" delivery.

A question and answer period followed Kozlowski's remarks. An audience member asked if cigarette companies are manipulating the nicotine content of cigarettes. Kozlowski responded that "that issue . . . is not a major issue." He stated that "ventilation blockage is far more important."

A second questioner asked whether all light and ultra-light cigarettes are ventilated. Kozlowski responded that they are, "at least to some degree." He added that "blocking vents is the gateway to a satisfying smoke."

C. Benowitz

Neil Benowitz proposed an aggressive regulatory program for tobacco products premised on the existence of an "addiction threshold" for nicotine; the ultimate goal of this program is the elimination of tobacco products from American society.[3/] The prepared presentation was largely identical

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3/ Benowitz and Jack Henningfield have advocated this approach in an article that appeared in the New England Journal of Medicine last year. Evidently, they have authored an expanded article that will appear this year in the British Journal of Addiction.

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to his remarks at the ASCPT meeting the previous week.[4/] Benowitz once again suggested that cigarettes are addictive, and that it might be possible to prevent nicotine addiction by reducing the amount of nicotine in cigarettes by government fiat.

In his SRNT presentation, Benowitz added a new slide showing the decline in the "tar" and nicotine yields of American cigarettes from the 1950s to the present. He claimed that low yield cigarettes artificially depress this curve, because these products actually deliver the same amount of "tar" and nicotine as regular cigarettes. Benowitz did concede, however, that ultra-low yield cigarettes actually deliver about 30% less "tar" and nicotine per cigarette than regular cigarettes.

Benowitz quickly worked his way into his proposal to restrict the nicotine content of cigarettes to .6 mg of nicotine per cigarette. Benowitz once again made his claim that a cigarette containing no more than .6 mg/nicotine would "not be addicting," based on a number of assumptions derived from chippers' smoking patterns.

A question and answer session followed Benowitz's presentation. The first questioner asked if Benowitz could safely rely on data extrapolated from chippers. Benowitz replied that there are "no data available to test" whether

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4/ See Memorandum of March 21, 1995 (providing an overview of Benowitz's presentation at the ASCPT meeting).

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chippers are representative of smokers as a group. He said that there "is probably some threshold" because people exposed to ETS do not become addicted to nicotine. However, he said that based on the available evidence we "can't know for sure" whether an addiction threshold actually exists. Jack Henningfield then stopped the Q & A, stating that the program was running late.

D. John Slade

John Slade treats patients who wish to stop smoking, and reported on his clinical experiences in smoking cessation programs. At the outset of his remarks, Slade admonished the crowd to use the term "nicotine abstinence" rather than "smoking cessation" when referring to the end point for nicotine treatment programs.

Slade traversed some of the ground covered by Kozlowski and Benowitz, criticizing the FTC testing method and arguing that ventilation holes make low and ultra low-yield cigarettes misleading. He then proposed "exploratory research on nicotine maintenance," including study of nicotine delivery systems, nicotine analogs, and the distribution system for nicotine-containing products.

Slade argued that the government must become expert in nicotine delivery systems and then "impose standards on the industry." He emphasized the importance of studying the cognitive and motor effects of nicotine as part of this program.

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Slade suggested that nicotine-containing products should be available only to existing smokers, and denied to non-smokers. In this regard, he suggested that nicotine-containing products be scheduled as class III or IV drugs and be limited to prescription sales. He conceded, however, that "low nicotine content products" might be made available over the counter, but emphasized that stronger products must be available only by prescription.

He characterized the low-yield model of regulation as "a failure." Slade said that a prescription regime is the only effective means of regulating nicotine-containing products.

Slade concluded by showing photographs of Canadian, Australian, and Thai cigarette packages, all of which have very large health warnings. Slade advocated the adoption of similar measures in the United States. Because of the late hour, there was no Q & A session for Slade.

E. John Hughes

John Hughes began his presentation by noting that he has accepted monies from certain pharmaceutical companies with an interest in nicotine replacement therapies. Hughes then argued that nicotine replacement therapy should be used more frequently to assist those trying to quit smoking.

Hughes advocated the other-the-counter sale of nicotine replacement products. In support of this position, he noted that many people trying to quit will not seek out a

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prescription for such products, and that OTC availability would facilitate more successful quit attempts.

He identified a number of potential opportunity costs that might accompany OTC availability of nicotine replacement therapies, including (1) the absence of physician supervision, (2) increased risk of misuse, and (3) undermining the general social disapprobation of smoking.

F. Charles Gruder

Charles Gruder oversees the California Tobacco-Related Disease Research Program. This program distributes Proposition 99 money to tobacco-related research projects. Gruder described the mechanics of Proposition 99 (i.e., a new 25¢ tax/pack and a statutory allocation scheme for the proceeds, with monies deposited to six discrete accounts).

Gruder complained bitterly that the Legislature had reallocated Proposition 99 monies from tobacco-related research to primary care services. Gruder claimed that an alliance of medical doctors, hospitals, and tobacco interests conspired to raid the Tobacco-Related Diseases Research Account. He expressed delight in a recent Superior Court case, which he claims overturned this reallocation of funds.[5/]

According to Gruder, the reallocation of funds "hamstrung" the program's research activities. His office has

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5/ Gruder claimed that Superior Court Judge Robert Warren issued the decision orally, promising that a written opinion would follow.

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funded only 44 grants this fiscal year, out of 80 approved projects. Gruder expressed great frustration over the reduction in funding, and blamed his predicament on the tobacco industry.

G. Audience Comments

Because this session ran significantly overtime, audience members were allowed to make brief comments, but did not ask questions. The first comment came from a Swedish doctor who suggested that nicotine/"tar" ratios should be increased, thereby reducing the harmful effects of "tar." He also advocated additional labelling requirements, specifically including "the harmful components of 'tar.'" In this regard, he suggested that Benowitz's proposal would not work, because net yields would remain constant.

The second comment came from a U.S. Air Force physician, who stated that 76% of smokers who enlist in the Air Force begin smoking again after completing a compulsory smoke-free six weeks of basic training. Furthermore, following basic training, 6% of non-smoking recruits become smokers. He argued that this evidence suggests that greater focus needs to be placed on the behavioral reasons people smoke than on nicotine.

Dr. M.J. Rand then stood up to criticize the entire program. According to Dr. Rand, "75% of the information I have received today pertained to U.S. history and politics." Noting that he had flown over 5,000 miles to attend the

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conference, he issued a "plea for this society to stay with scientific matters so far as possible."

The fourth commenter, reacting to Benowitz's presentation, suggested that a high nicotine/low "tar" cigarette would be a good middle ground. Benowitz responded that this approach might reduce "tar" intake by 20-30%, but that non-addicting cigarettes would provide far greater gains. However, Benowitz said that if his proposal is not feasible, "high nicotine/low 'tar' cigarettes are a concept worth considering." However, he believed that the taste of such a product would "put people off."

V. Federal Grants Session.

The first session on Saturday, March 25, 1995 was devoted to federal funding for nicotine research. Representatives of NIDA, NICHD, and NIAAA gave presentations.

A. Norman Krasnegor (NICHD)

Krasnegor reported that the National Institute for Child Health Development maintains an interest in nicotine research because of the alleged effects of smoking on children and expectant mothers. Evidently, NICHD currently underwrites studies of the effects of smoking on pregnant women and children. However, Krasnegor emphasized that NICHD's funds for these projects are relatively modest.

Krasnegor noted that "unintentional injuries" are the greatest source of harm to children, and suggested that exposure to tobacco smoke and youth smoking should be viewed

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as an "unintentional injury." According to Krasnegor, such an approach would permit NICHD to spend additional monies on anti-smoking activities.

B. John Allen (NIAAA)

John Allen represented the National Institute of Alcohol and Alcohol Abuse, a federal agency that investigates the causes and treatment of alcoholism and related diseases. Because many alcoholics are also smokers, Allen believes that the smoking and drinking behavior should be studied conjunctively. He reported that NIAAA has tentatively budgeted $2 million to fund 8-10 projects on alcohol and nicotine dependence. Allen said that funding for an additional 8 projects might also be allocated.

NIAAA will be releasing an RFA (research funding announcement) in the coming weeks with details regarding these grants. Allen hopes that the RFA will "jump start" NIAAA's role in funding new tobacco-related research projects.

C. David Johnson (NIDA)

David Johnson of the National Institute of Drug Abuse noted that his agency funds 22% of all proposals for nicotine research that it receives. He stated that the new director, Allen Leshner, wants to increase NIDA's profile in the area of tobacco control. NIDA funded 84 projects in 1994, with a total cost of $19 million (or 7.8% of the agency's total funds).

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Allen said that NIDA is interested in funding new projects, and would welcome applications from scientists interested in pursuing nicotine research. In addition, NIDA will make a new program announcement (this is not an RFA) this fall at the Society for Neuroscience's annual meeting. Evidently, NIDA hopes to establish a new bureau that will focus on smoking and nicotine dependence.

VI. Genetics and Smoking Behavior.

Five panelists held a discussion of the role of genetics in predicting smoking status. Dr. Andrew Heath presented data showing that personality traits do not accurately predict smoking status; from this, he suggested that genetic influences might be weak. On the other hand, Dr. Allen Collins presented data showing that different breeds of mice react differently to the same quantity of nicotine. Significantly, he found predictable ranges of response from breed-to-breed. Based on this evidence, he suggested that there must be a genetic role in smoking status.

Dr. Ernest Noble studied the presence of two alleles in a group of subjects, trying to determine whether the A-1 and A-2 alleles predicted smoking status. He concluded that a gene might exist that would serve as a predictor for smoking status in women, but not in men.

Dr. Gerald McClearn, like Allen Collins, presented data derived from mice studies. According to McClearn, his studies demonstrate that "genes and environment are co-acting"

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forces in determining smoking status. He believes that genetic coding exists for smoking status, and that environmental and/or genetic influences trigger a genetic predisposition to smoke. However, the relationship between smoking is "non-linear," and "multiple feedback loops exist."

A question and answer session followed, in which audience members submitted written questions to the panelists. The first question asked why personality variables do not correlate with smoking status, if personality is a function of genetics. Dr. Heath responded that there are over 100,000 genes at work, and that "the paths are polymorphic." Heath said that his study simply picked the wrong gene.

The second question asked whether Heath's approach overstated the genetic role, and asked whether non-smoking spouses tended to begin smoking if they were married to a smoker. Heath replied that one has to be careful in selecting controls, and that he used twins for independent controls. The response seemed to be a non-sequitur, but the format did not permit a follow up question.

VII. <u>Master Lecture by Benowitz.</u>

Dr. Neil Benowitz presented the first annual SRNT "master lecture." He spoke on "Recent Developments in Nicotine Pharmacology." Benowitz's presentation focused almost completely on the pharmacology of nicotine, and did not address larger social policy and regulatory issues associated with tobacco use.

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He began his lecture by discussing how the body metabolizes nicotine. According to Benowitz, the body metabolizes nicotine into cotinine, nornicotine, N-imminium ion, and nicotryine. Approximately 8% of nicotine becomes cotinine; however, this figure varies from person to person. He also noted that smokers metabolize nicotine more slowly than non-smokers.

Benowitz said that he had adduced "no evidence of metabolic tolerances" that would explain the increase and then levelling-off of nicotine consumption exhibited by many smokers. He also claimed that blacks have higher cotinine levels than whites, even though they consume the same amount of nicotine, perhaps because they metabolize cotinine more slowly than whites.

Benowitz then turned to a description of the pharmokinetics and pharmacodynamics of nicotine, which he claimed to be controlled by smoking behavior. According to Benowitz, nicotine affects the brain by facilitating the release of neurotransmitters, including serotonin, dopamine, and norepinephrine.[6/]

He then described a patient who self-administered a nicotine-based insecticide to treat an infestation of skin mites. Upon arrival at the hospital, she had 200 mg/ml of nicotine in her blood. She reported nausea, headache, and a

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6/ Benowitz used the same slide to demonstrate this point that he used at the ASCPT meeting a week earlier.

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racing pulse. At discharge a week later, she had a 300 mg/ml nicotine blood level, but was not sick. Benowitz said that this case study demonstrates that acute tolerance to nicotine develops very quickly.

Benowitz then presented a chart with an equation that ostensibly showed the properties of a hypothetical nicotine-antagonist substance, which tracked the parameters of tolerance to nicotine. He also claimed data that suggests cotinine has a negative effect on cognitive function.

In closing, Benowitz observed that a good deal more study was necessary before nicotine's effect on the body would be properly understood. A question and answer session followed.

The first questioner asked why the body retains nicotine. Benowitz responded that human tissues tend to retain nicotine; furthermore, a low dose is absorbed more effectively than a high dose.

The second questioner asked whether Benowitz had done any research on nicotine inhibitors. Benowitz said that he does not know of any nicotine inhibitors, but that work is being done on this topic.

Dr. Domino then asked if Benowitz "controlled for urinary Ph in his studies." Benowitz stated that he had, and that the nicotine excreted in urine is usually less than 10% of the nicotine consumed. Dr. Domino added that he has given cotinine to cats, and that at levels 1000% higher than

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nicotine, the cotinine provoked a response that mimicked the animals' response to nicotine.

VIII. **Second Annual SRNT Meeting.**

The Second Annual SRNT Conference will be held on March 15-16, 1996, in Washington, D.C. Materials regarding this conference can be obtained by calling (301) 251-2792.

Ron Krotoszynski, Jr.

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